Impact of targeting interleukin-13 on *Staphylococcus aureus* colonization: results from a Phase 3, randomized, double-blind, placebo-controlled trial of tralokinumab in adult patients with atopic dermatitis

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Background

- Atopic dermatitis is a chronic inflammatory skin disease with a high disease burden and a multifactorial pathogenesis, characterized by skin barrier disruption and immune dysregulation[1,2]
- Increased levels of type 2 cytokines (including interleukin [IL]-13) and skin barrier dysfunction collectively lead to microbial dysbiosis and *Staphylococcus aureus* colonization[3-5]
  - This dysbiosis is associated with greater atopic dermatitis severity and correlates with atopic dermatitis flares[6]
- Tralokinumab is a first-in-class, fully human, monoclonal antibody that binds with high affinity to and specifically neutralizes IL-13
- Tralokinumab demonstrated efficacy compared with placebo in a Phase 2b trial (NCT02347176) and in the recent ECZTRA 1 Phase 3 trial (NCT03131648)[7,8]

Objective

- To characterize the effect of tralokinumab treatment on *S. aureus* colonization

Methods

Study design and patients

- ECZTRA 1 (NCT03131648) was a multinational, double-blind, randomized, placebo-controlled, 52-week trial[8]
- Patients with moderate-to-severe atopic dermatitis were randomized 3:1 to subcutaneous tralokinumab 300 mg or placebo every 2 weeks for an initial 16 weeks
- Patients from select ECZTRA 1 study sites were invited to participate in microbiome characterization

Microbiome characterization

- Changes in skin colonization by *S. aureus* at week 16 in patients was an exploratory endpoint of the ECZTRA 1 trial
- Absolute abundance of *S. aureus* on lesional skin was assessed by extracting DNA from skin swabs, followed by quantitative polymerase chain reaction targeting the *femA* gene
- Serum biomarkers were also measured:
  - IL-13 and IL-22 in Singulex Errena Array
  - Chemokine (C-C motif) ligand (CCL17) by enzyme-linked immunosorbent assay

Statistical analysis

- Spearman correlation was used to assess the correlations between *S. aureus* colonization and Eczema Area and Severity Index (EASI) score, and serum biomarkers
- The ratio between treatment groups relative reduction in cutaneous *S. aureus* from baseline to week 16 was assessed by a t-test of changes in log-transformed values

Results

Patient demographics

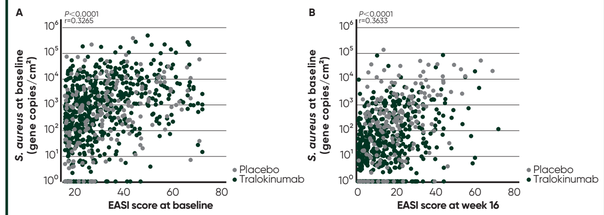
- Baseline demographics were well balanced across treatment groups **(Table 1)**
- 92.5% of placebo-treated patients and 92.0% of tralokinumab-treated patients were *S. aureus* positive at baseline

Table 1. Patient demographics and baseline characteristics

Characteristic	Placebo (n=199)	Tralokinumab q2w (n=603)
Median age, years (IQR)	37.0 (26.0–49.0)	37.0 (27.0–48.0)
Male, n (%)	123 (61.8)	351 (58.2)
Race, n (%)		
White	138 (69.3)	426 (70.6)
Black	18 (9.0)	41 (6.8)
Asian	40 (20.1)	120 (199)
Other or missing data	3 (1.5)	16 (2.6)
Median disease duration, years (IQR)	28.0 (18.0–41.0)	27.0 (19.0–38.0)
Median affected body surface area, % (IQR)	52.5 (31.0–77.0)	50.0 (33.0–70.0)
Median EASI (IQR)	30.3 (22.0–41.5)	28.2 (21.3–40.0)
IGA-4, n (%)	102 (51.3)	305 (50.6)
S. aureus PCR+ patients at baseline, n (%)	184 (92.5)	555 (92.0)

IQR, interquartile range; q2w, every 2 weeks; PCR, polymerase chain reaction.

Figure 1. *S. aureus* colonization correlation with disease severity



IQR, interquartile range; q2w, every 2 weeks; PCR, polymerase chain reaction.

Correlation of *S. aureus* and EASI score

- Levels of *S. aureus* colonization correlated with disease severity (EASI score) at baseline (r=0.3265, *P*<0.0001) and week 16 (r=0.3633; *P*<0.0001) **(Figure 1)**

Correlation of *S. aureus* and serum biomarkers

- Levels of *S. aureus* colonization correlated with levels of IL-13 (baseline only), CCL17, and IL-22, at baseline and week 16 (r=0.3329–0.4340; *P*<0.0001) **(Figure 2)**
  - As the therapeutic target of tralokinumab, IL-13 levels could not be measured at week 16

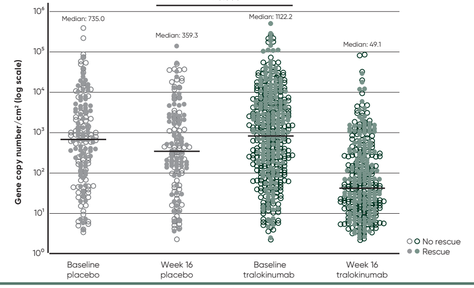
Reduction in *S. aureus* colonization from baseline to week 16

- A 10-fold greater reduction in *S. aureus* colonization was seen for tralokinumab versus placebo in the full population regardless of rescue medication use (ratio=0.09; *P*<0.0001) **(Figure 3)**
- In an analysis excluding patients who used rescue medication, a significant reduction in *S. aureus* colonization for tralokinumab versus placebo-treated patients was observed (ratio=0.12; *P*<0.0001)
  - In ECZTRA 1, rescue medication (topical corticosteroids in the majority of patients) was used by 35.8% of tralokinumab and 46.2% of placebo patients

S. aureus colonization at week 16 in EASI-75 responders

- Patients who achieved EASI-75 with tralokinumab had lower median *S. aureus* colonization at week 16 compared with patients who achieved EASI-75 with placebo (22.9 vs. 240.8 gene copy number/cm²) **(Figure 4)**
- There was a significant reduction from baseline to week 16 in median count for tralokinumab versus placebo in EASI-75 responders (−96.6%; *P*<0.0001 vs. +34.2%; not significant)

Figure 3. Median *S. aureus* colonization at baseline and week 16



In ECZTRA 1, the rescue medication was topical corticosteroids in 94% of tralokinumab patients and 98% of placebo patients.

Figure 4. Median *S. aureus* colonisation in EASI-75 responders (week 16)

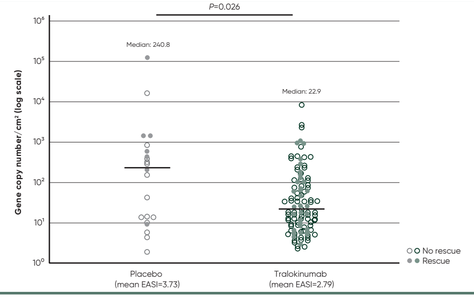
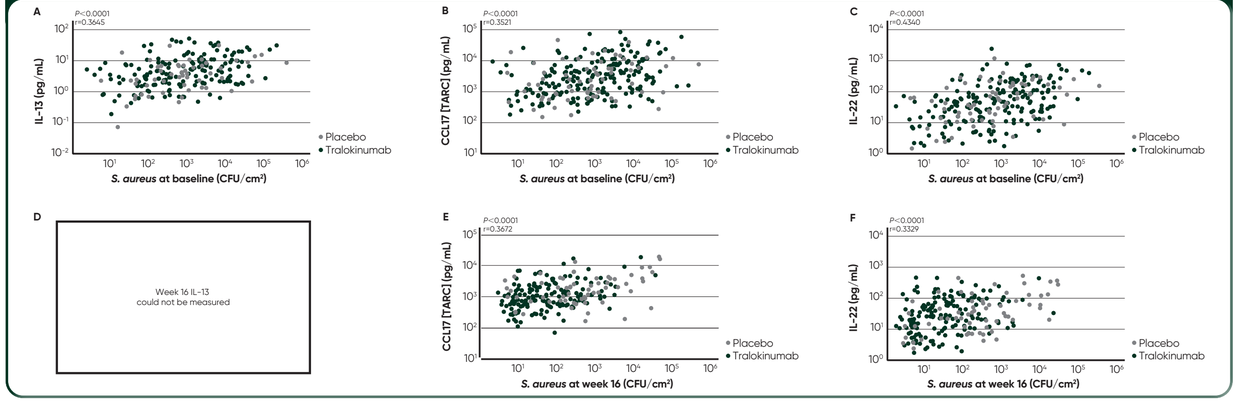


Figure 2. *S. aureus* colonization correlation with select serum biomarkers



Correlations refer to the combined placebo and tralokinumab population. CFU, colony forming units; TARC, thymus and activation regulated chemokine

Conclusions

- Levels of *S. aureus* colonization correlated positively with EASI score and serum levels of several atopic dermatitis biomarkers, including IL-13, IL-22, and CCL17
- Treatment with tralokinumab was associated with a significantly greater reduction in *S. aureus* colonization in lesional skin compared with placebo in adult patients with moderate-to-severe atopic dermatitis
  - This supports a previous study demonstrating an *S. aureus* colonization reduction with tralokinumab[9]
- Though the causal relationship between atopic dermatitis inflammation and dysbiosis remains unclear, the results shown here suggest the reduction of *S. aureus* colonization is due to specific neutralization of IL-13 with tralokinumab and not due merely to atopic dermatitis skin improvement

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Disclosures

Thomas Bieber has been a speaker, and/or consultant, and/or investigator for: AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Astellas, BioVerSys, Böhringer-Ingelheim, Celgene, Daichi-Sankyo, Dermavant/Roivant, DermTreat, DS Pharma, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incytes, Kymab, LEO, Lilly, L'Oréal, MenloTx, Novartis, Pfizer, Pierre Fabre, RAPT/FLX Bio, Sanofi/Regeneron, and UCB

Lisa A. Beck has been a consultant for AbbVie, Allakos, Arena Pharma, Astra-Zeneca, Connect Biopharma, LEO Pharma, Lilly, Novartis, Pfizer, Rapt Therapeutics, Regeneron, Sanofi, UCB and Vimalan; an investigator for Abbvie, LEO Pharma, Pfizer, Regeneron, and Sanofi; and owns stock in 3M, Gilead, and Medtronics

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Anders Rosholm is currently an employee of Orphazyme and was an employee of LEO Pharma at the time of the ECZTRA 1 trial and analysis

Mads Røpke and Karen Veverka are employees of LEO Pharma

Amy Paller has been an investigator for AbbVie, Anaptysbio, Celgene, Lilly, Galderma, Incyte, LEO Pharma, Janssen, Novartis, and Regeneron; and a consultant with honorarium for Almirall, Amgen, Asana, Boehringer-Ingelheim, Castle Creek, Celgene, Dermavant, Dermira, Lilly, Exicure, Forte, Galderma, Lenus, LEO Pharma, MEDA Corp, Meiji Seika, Novan, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, and Sol Gel

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